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Meta-analysis of stomatitis in clinical studies of everolimus: incidence and relationship with efficacy

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Background: Everolimus, an oral mammalian target of rapamycin (mTOR) inhibitor, is used to treat solid tumors and tuberous sclerosis complex (TSC). Stomatitis, an inflammation of the mucous membranes of the mouth, is a common adverse event associated with mTOR inhibitors, including everolimus. We conducted a meta-analysis of data from seven randomized, double-blind phase 3 clinical trials of everolimus to determine the clinical impact of stomatitis on efficacy and safety.

Patients and methods: Data were pooled from the safety sets of solid tumor [breast cancer (BOLERO-2 and BOLERO-3), renal cell carcinoma (RECORD-1), carcinoid tumors (RADIANT-2), and pancreatic neuroendocrine tumors (RADIANT-3)] and TSC studies (EXIST-1 and EXIST-2). Data from solid tumor trials and TSC trials were analyzed separately.

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Results: The rate of stomatitis was 67% in the solid tumor trials (973/1455 patients) and 70% in the TSC trials (110/157 patients). Most stomatitis events were grade 1/2, with grade 3/4 events reported in only 9% (solid tumor trials) and 8% (TSC trials) of patients. Low TSC patient numbers prevented an in-depth evaluation of stomatitis and response. In the solid tumor trials, most first stomatitis episodes (89%; $n = 870$) were observed within 8 weeks of starting everolimus. Patients with stomatitis occurring within 8 weeks of everolimus initiation had longer progression-free survival (PFS) than everolimus-treated patients without stomatitis in BOLERO-2 {8.5 versus 6.9 months, respectively; hazard ratio (HR), 0.78 [95% confidence interval (CI), 0.62–1.00]} and RADIANT-3 [13.9 versus 8.3 months, respectively; HR, 0.70 (95% CI, 0.48–1.04)]. A similar trend was observed in RECORD-1 [HR, 0.90 (95% CI, 0.66–1.22)] and RADIANT-2 [HR, 0.87 (95% CI, 0.61–1.22)] but not in BOLERO-3 [HR, 1.01 (95% CI, 0.75–1.36)].

Conclusions: Stomatitis did not adversely affect PFS, supporting the administration of everolimus in accordance with standard management guidelines.

Key words: everolimus, stomatitis, breast cancer, renal cell carcinoma, pancreatic neuroendocrine tumors, tuberous sclerosis complex

introduction

Everolimus is an oral mammalian target of rapamycin (mTOR) inhibitor that is commonly used in the treatment of cancer [renal cell carcinoma (RCC), pancreatic neuroendocrine tumors (pNET), and hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) breast cancer] as well as tuberous sclerosis complex (TSC) [1]. One of the most common adverse events (AEs) associated with mTOR inhibitors is stomatitis, an inflammation of the mucous membranes of the mouth [1, 2]. In particular, mTOR inhibitor-associated stomatitis is similar to aphthous ulceration, characterized by small, distinct ovoid ulcers that are gray and surrounded by an erythematous ring, and which affect the non-keratinized mucosa of the oral cavity. Stomatitis is clinically distinct from mucositis, which is associated with conventional chemotherapy or ionizing radiation and generally presents as non-uniform erythematous and ulcerated lesions that may extend to the gastrointestinal tract [3].

The clinical impact of stomatitis on efficacy is of particular interest, and greater understanding of this AE may help physicians anticipate and manage this event. Therefore, we conducted a meta-analysis of individual patient data from seven randomized, double-blind phase 3 clinical trials of everolimus in patients with advanced breast cancer, pNET, and RCC as well as in patients with TSC [4–10]. Here, we report on the incidence, time to occurrence, and severity of stomatitis and assess the impact on clinical outcome. Our results show that stomatitis did not adversely affect progression-free survival (PFS) and support the administration of everolimus in accordance with standard management guidelines.

methods

studies

Data were pooled from the safety sets (patients who received ≥1 dose of study drug) of seven randomized, double-blind phase 3 clinical trials of everolimus conducted in patients with advanced solid tumors and TSC (Table 1). Due to inconsistencies regarding the precise terms used to report AEs in clinical trials, a broad inclusive definition was applied to capture stomatitis events that may not have been recorded as such. The meta-analysis included patients with AEs of aphthous stomatitis, gingival swelling, gingival pain, gingival ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, mucosal ulceration, stomatitis, or tongue ulceration, per the preferred terms of the Medical Dictionary for Regulatory Activities version 16.0. Events were included in the analysis if they occurred during the double-blind treatment period or up to 28 days after the last dose of study drug.

Stomatitis was characterized and graded per Clinical Trials Criteria for Adverse Events v3.0, and defined as follows: minimal symptoms with normal diet, not requiring medical intervention (grade 1); symptomatic, can eat and drink a modified diet, respiratory symptoms requiring medical intervention but not interfering with activities of daily living (grade 2); symptomatic, affecting ability to eat and drink adequately, respiratory symptoms affecting activities of daily living (grade 3); symptoms with life-threatening consequences (grade 4).

analyses

Solid tumor trial data were analyzed separately from TSC trial data. Time to first occurrence of stomatitis was defined as the time from the start of study treatment to the date of the first occurrence of stomatitis. In the absence of stomatitis, patients were censored if they died, received new anticancer therapy, discontinued double-blind study treatment, or were still receiving treatment at the cutoff date. Recurrent stomatitis was defined as a second stomatitis event starting ≥2 days after resolution of the first event. Time to recurrent stomatitis was defined as the date of the start of recurrence minus the date of first occurrence resolution. The Kaplan–Meier methods were used to analyze time to the first episode of stomatitis and time from the end of the first episode to the second episode of stomatitis.

The association between stomatitis and PFS was evaluated by comparing investigator-assessed PFS between patients with and without stomatitis within 8 weeks (i.e. 56 days) of the start of everolimus. The 8-week interval was selected to be long enough to include most first stomatitis episodes (89%; $n = 870$) and as it constitutes an easy-to-understand time interval (8 weeks = 2 months). Stratified Cox regression analyses used stratification factors as defined in individual study protocols and were adjusted for additional known baseline prognostic factors, including Eastern Cooperative Oncology Group performance status of 0 versus 1–2 at baseline and Asian versus non-Asian for BOLERO-2; Asian versus non-Asian for RADIANT-3 and BOLERO-3; Karnofsky performance status of ≤80 versus >80 for RECORD-1; and age <65 versus ≥65 years, Caucasian yes versus no, World Health Organization performance status of 0 versus 1 or 2, and lung origin yes versus no for RADIANT-2. Hazard ratios (HRs) were corrected for the confounding effect of duration of exposure using a bootstrap-based method.

Table 1. Phase 3 clinical studies included in the meta-analysis

Study	Patient population	Treatment arms	n^a
Solid tumor studies			
BOLERO-2 [4]	HR+/HER2− advanced breast cancer	Everolimus (10 mg/day) + exemestane	482
		Placebo + exemestane	238
BOLERO-3 [5]	HER2+ advanced breast cancer	Everolimus (5 mg/day) + trastuzumab + vinorelbine	280
		Placebo + trastuzumab + vinorelbine	282
RADIANT-2 [6]	Advanced carcinoid tumor	Everolimus (10 mg/day) + octreotide LAR	215
		Placebo + octreotide LAR	211
RADIANT-3 [7]	Advanced pNET	Everolimus (10 mg/day)	204
		Placebo	203
RECORD-1 [8]	Advanced RCC	Everolimus (10 mg/day)	274
		Placebo	137
TSC studies			
EXIST-1 [9]	TSC (SEGA)	Everolimus (titrated to blood trough concentration of 5 to 15 ng/ml)	78
		Placebo	39
EXIST-2 [10]	TSC (renal angiomyolipoma)	Everolimus (10 mg/day)	79
		Placebo	39

HER2−, human epidermal growth factor receptor 2-negative; HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor-positive; LAR, long-acting repeatable; pNET, pancreatic neuroendocrine tumors; RCC, renal cell carcinoma; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis complex.
[a]Number of patients in the safety set.

results

solid tumor trials

incidence and risk. A total of 1455 patients treated with everolimus in the solid tumor trials were included in the analysis (Table 1). Of these, 973 patients (67%) experienced stomatitis, with most of all first episodes (89%; $n = 870$) occurring within 8 weeks of the start of everolimus. The incidence of stomatitis ranged from 59% in RECORD-1 to 71% in BOLERO-3. By comparison, the incidence in the 1071 patients in the control arms was 19% [range, 11% in RECORD-1 (placebo) to 29% in BOLERO-3 (placebo + trastuzumab + vinorelbine)]. Of the 973 patients treated with everolimus who experienced an initial stomatitis event, 388 (40%) experienced a second episode.

The Kaplan–Meier plots and exploratory Cox models stratified by study were used to assess the influence of body mass index (BMI), age, and history of diabetes on time to the first stomatitis event. Stomatitis rates tended to be lower in patients with BMI > 25 kg/m^2 than in patients with BMI ≤ 25 kg/m^2 (64% and 70%, respectively). Additionally, the median time to the first stomatitis event was longer for patients with BMI > 25 kg/m^2 than in those with BMI ≤ 25 kg/m^2 (29 and 20 days, respectively), with an estimated HR of 0.83 [95% confidence interval (CI), 0.73–0.94; supplementary Figure S1A, available at Annals of Oncology online]. These results may be related to exposure. Patients ≥65 years of age had a slightly lower incidence of stomatitis than patients <65 years of age (64% and 68%, respectively) and a slightly longer median time to the first stomatitis event [29 and 22 days, respectively; HR, 0.90 (95% CI, 0.78–1.03); supplementary Figure S1B, available at Annals of Oncology online]. However, this may be confounded by an indication effect since BOLERO-3, which had the lowest median age, had the highest rate of stomatitis. Additionally, we noted that patients with no prior history of diabetes had an apparently higher rate of stomatitis than patients with prior diabetes (68% and 59%, respectively) and a shorter median time to the first stomatitis event [23 and 54 days, respectively; HR, 1.27 (95% CI, 1.04–1.55); supplementary Figure S1C, available at Annals of Oncology online]; this result could also be confounded by indication (breast cancer trials had fewer patients with a history of diabetes and higher rates of stomatitis) or other factors.

grade and study treatment impact. Although the overall incidence of stomatitis of any grade in the everolimus-containing arms was 67%, most stomatitis events were grade 1/2, with grade 3/4 events reported in 9% of patients and only 1 patient experiencing grade 4 stomatitis (0.1%). Among the 388 patients who experienced at least two stomatitis events, the rate of grade 3/4 episodes was lower at the time of recurrence (7.2% versus 12.1% for the initial episode; Figure 1).

Stomatitis led to dose reductions and/or interruptions in 236 of 973 patients (24%) during episode 1 and 88 of 388 patients (23%) during episode 2. During the first stomatitis episode, dose reductions and/or interruptions were more frequent in patients enrolled in breast cancer trials (32% in BOLERO-2 and 34% in BOLERO-3 versus 12%–17% in the non-breast cancer studies), in which everolimus was administered in combination with other agents. Dose reductions were also more frequent in patients who experienced grade 3/4 stomatitis (87% versus 17% for grade 1/2). Discontinuation due to stomatitis was reported in 2% of patients (25 of the 1455 everolimus-treated patients), after the first ($n = 14$), second ($n = 9$), third ($n = 1$), or fifth ($n = 1$) episode.

analyses of time to stomatitis event. Based on the Kaplan–Meier estimates, the rate of any-grade stomatitis was 60.8% (95% CI, 58.3%–63.3%) at 2 months, and the median time to

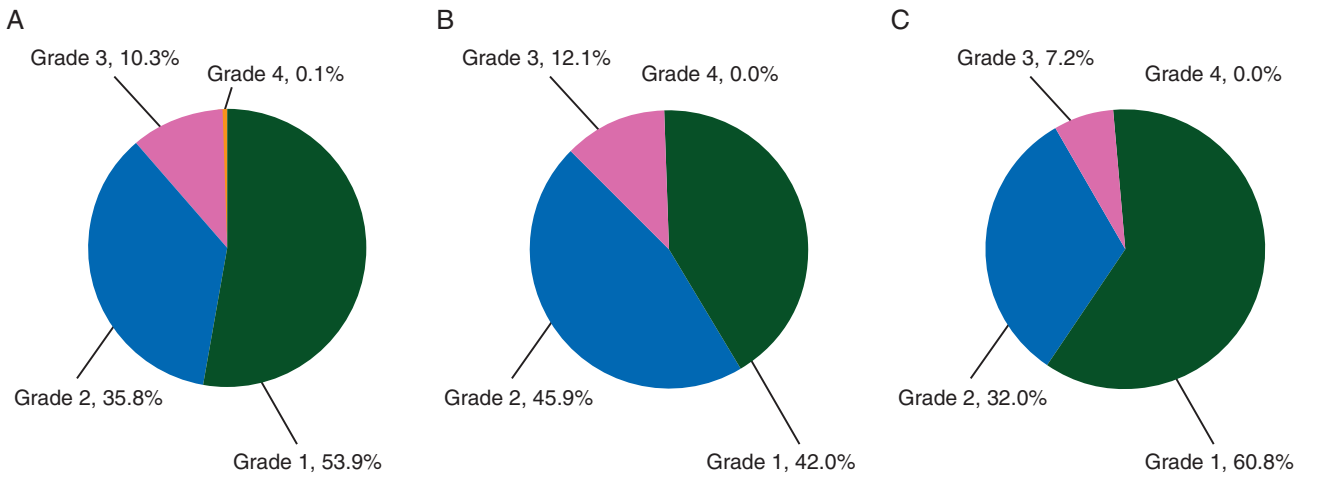

Figure 1. Grade of first and second stomatitis episodes in solid tumor trials. (A) First episode in patients with ≥1 stomatitis event ($n = 973$); (B) first episode in patients with ≥2 stomatitis events ($n = 388$); (C) second episode in patients with ≥2 stomatitis events ($n = 388$). Data shown are crude rates that do not account for study discontinuation.

the first episode was 0.8 months (95% CI, 0.7–1.0 months; Figure 2A). Among patients who experienced ≥1 stomatitis event (any grade), time to recurrence was longer than time to first occurrence, with a 2-month Kaplan–Meier estimate of 28.0%. The apparent time to recurrence was slightly shorter after grade 3/4 events (supplementary Figure S2, available at Annals of Oncology online).

impact on PFS. Compared with patients in the control arms in the solid tumor studies, PFS was longer in patients treated with everolimus, regardless of whether they experienced a stomatitis event within the first 8 weeks of treatment (Figure 3). Interestingly, in the BOLERO-2 breast cancer and RADIANT-3 advanced pNET trials, the occurrence of stomatitis within 8 weeks of everolimus initiation was associated with longer PFS than the absence of stomatitis in everolimus-treated patients. Specifically, in BOLERO-2, the median PFS was 8.5 versus 6.9 months for everolimus-treated patients with versus without stomatitis within 8 weeks, respectively [HR, 0.78 (95% CI, 0.62–1.00)]. In RADIANT-3, the median PFS was 13.9 versus 8.3 months for everolimus-treated patients with versus without stomatitis within 8 weeks, respectively [HR, 0.70 (95% CI, 0.48–1.04)]. A similar trend was observed in RECORD-1 [HR, 0.90 (95% CI, 0.66–1.22)] and RADIANT-2 [HR, 0.87 (95% CI, 0.61–1.22)] but not in BOLERO-3 [HR, 1.01 (95% CI, 0.75–1.36)]. A relationship between grade of stomatitis and efficacy was not seen; however, the relatively small number of grade 3/4 stomatitis events limits the interpretation of these data (data not shown).

TSC trials

Across the two TSC trials (EXIST-1 and EXIST-2), 110 of the 157 patients (70%) treated with everolimus reported stomatitis of any grade, including 12 patients (8%) with a grade 3/4 event. Stomatitis led to dose adjustment/interruption in 10 patients (6%) and was not reported to have led to study drug discontinuation in any patients. Based on the Kaplan–Meier estimates, the rate of any-grade stomatitis was 61.3% at 2 months, and the median time to the first episode was 1 month (Figure 2B). Due to the small number of patients in the TSC population, we were unable to evaluate the relationship between stomatitis and response.

discussion

Stomatitis is a common complication of mTOR inhibitor treatment. In our meta-analysis of phase 3 studies, we used a broad definition to capture stomatitis events not specifically categorized as such, and found that the overall rate (any grade) of the AE was similar across studies of four different advanced solid tumors (67%) and across the TSC trials (70%). We also noted that the incidence of grade 3/4 events was low (9% in solid tumor trials and 6% in TSC trials). Among patients who experienced two events ($n = 388$), the severity of the second event appeared to be lower than that of the first (grade 3/4 event rates of 7% and 12%, respectively), which could reflect the use of prophylactic measures and/or dose reduction. Indeed, dose reductions and/or interruptions due to stomatitis were more frequent in patients with grade 3/4 events and in patients enrolled in clinical trials of breast cancer. We noted, however, that drug discontinuation due to stomatitis was rare (2%). These results should be interpreted with caution, as they do not account for shorter duration of everolimus exposure in patients discontinuing due to disease progression or the use of reduced everolimus doses following a first event. Other factors, including dose (10 versus 5 mg/day) and treatment regimen (single versus multiple agent), may impact these results.

The onset of stomatitis was rapid (median, ≤1 month). At 2 months, the rate of stomatitis (any grade) was 60.8% in solid tumor trials and 61.3% in TSC trials. These data support the importance of early follow-up and awareness of AE management guidance in the approved prescribing information.

Of particular interest, the benefit of everolimus in patients who experienced stomatitis was consistent with that observed in the overall population. Additionally, stomatitis was associated with longer PFS in the BOLERO-2 and RADIANT-3 studies. A similar trend was reported in RECORD-1 and RADIANT-2

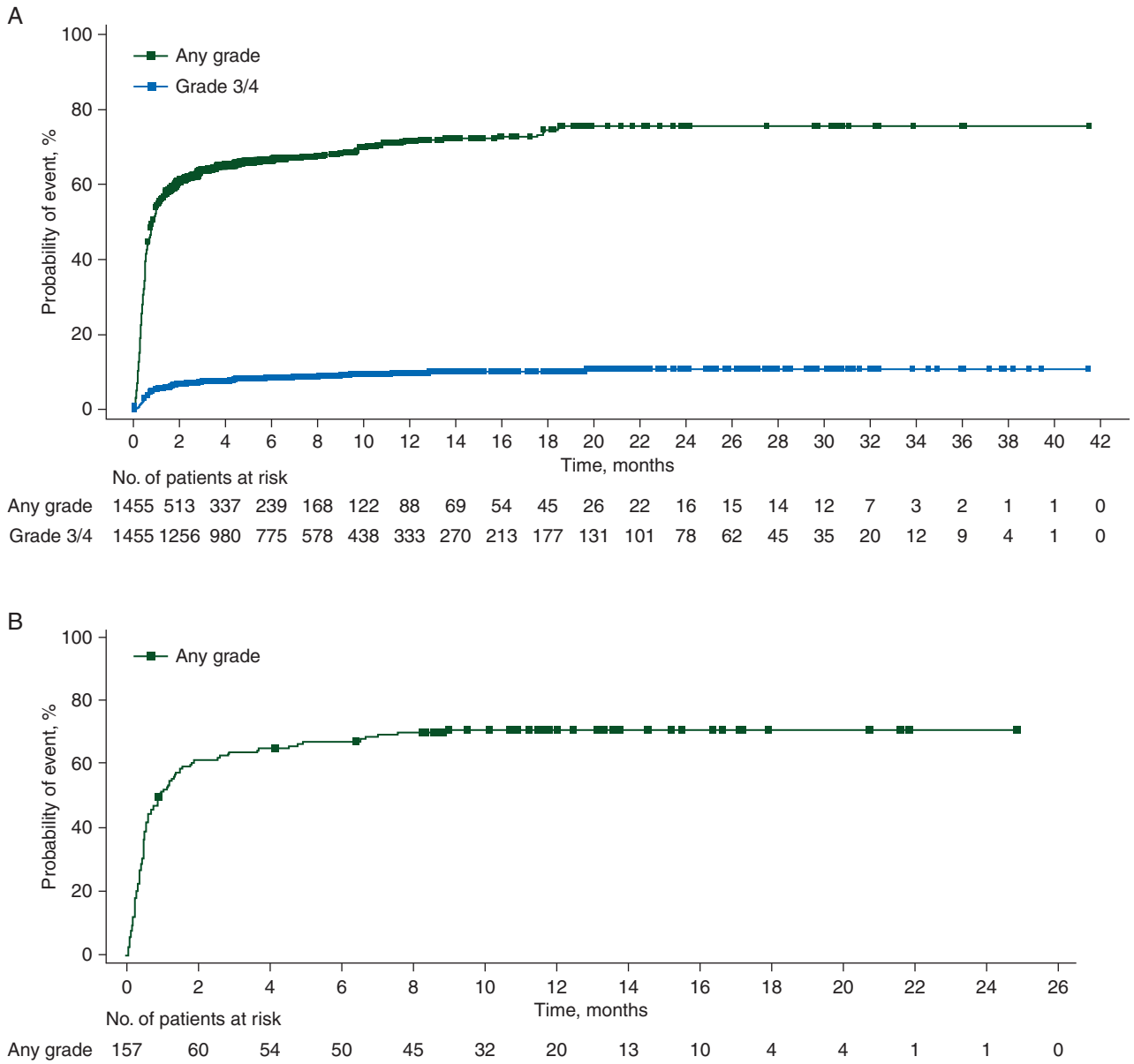

Figure 2. Time to first stomatitis event. The Kaplan–Meier estimates of time to the first stomatitis event in everolimus-treated patients in (A) solid tumor and (B) TSC trials. Symbols represent censoring times.

but not in BOLERO-3, which limits broader interpretation. The reason for the differences in findings between trials is unknown but may be due to differences in drug exposure and/or interaction with combination therapies. Moreover, the findings should be interpreted with caution due to the retrospective/exploratory nature of the analyses. Also, due to the small number of patients with TSC, an in-depth evaluation of the relationship between stomatitis and response was not possible in this population.

There was some evidence that patients with higher BMI (>25 kg/m^2) had slightly lower rates of stomatitis and longer onset to first occurrence than patients with lower BMI (≤25 kg/m^2), which may be related to lower exposure to everolimus in patients with higher BMI. The observed effects of age and history of diabetes on stomatitis rates and time to first stomatitis event may have been confounded by study indication or other factors and should be interpreted with caution.

conclusion

Overall, the results of this meta-analysis suggest that stomatitis did not adversely affect PFS. The findings suggest that with early follow-up (within 2 weeks), proactive management, and dose adjustments according to approved prescribing information in patients who experience stomatitis, everolimus can be administered with confidence regarding patient comfort, compliance, and safety. Indeed, in a study of patients with HR+ advanced breast cancer treated with everolimus and exemestane in German centers, 87% of patients received prophylactic stomatitis treatment. The reported rate of stomatitis (any grade) was

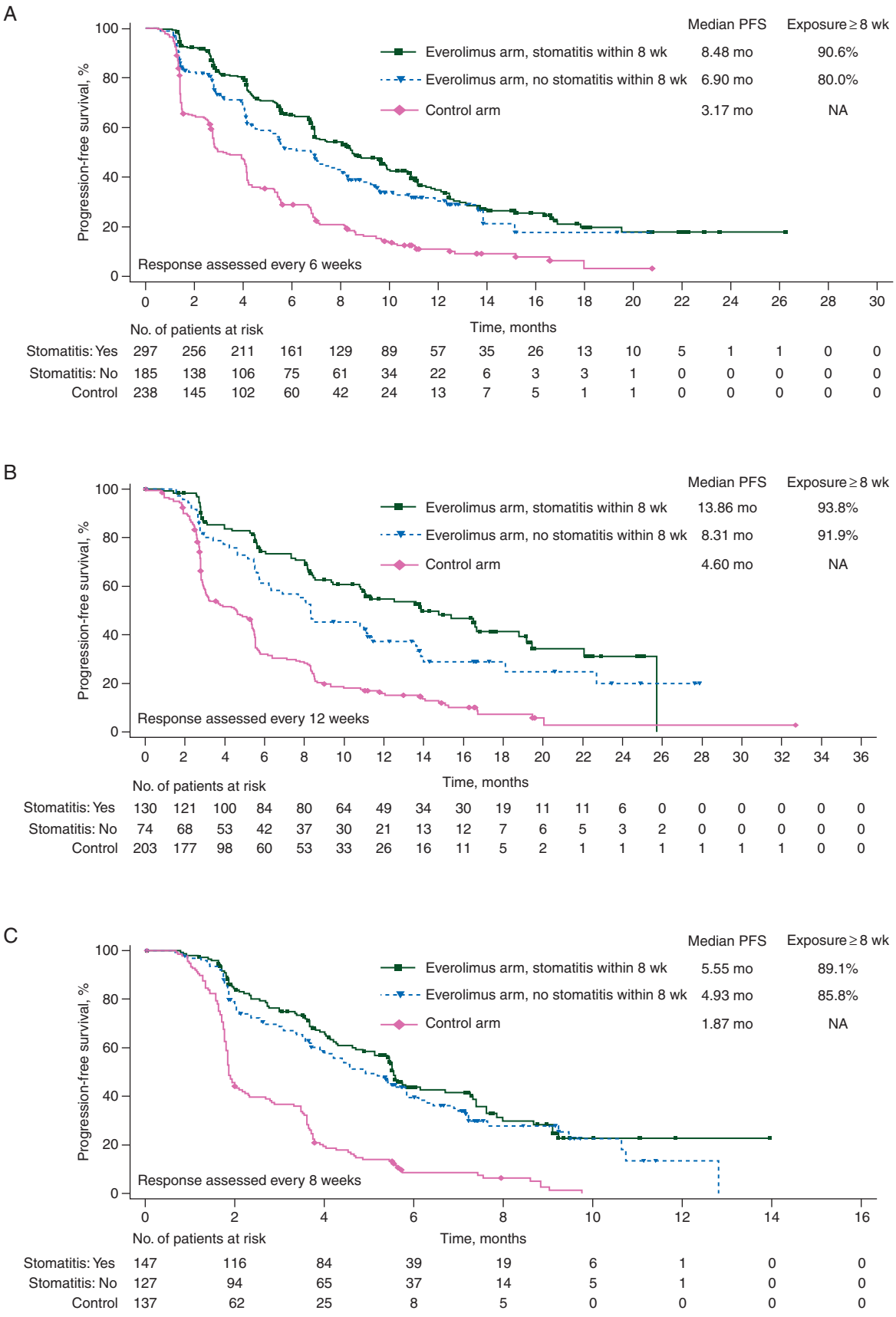

Figure 3. Association of stomatitis with PFS. The Kaplan–Meier estimates of PFS are shown for patients in the everolimus arms (with versus without stomatitis within 8 weeks) and control arms of the (A) BOLERO-2, (B) RADIANT-3, and (C) RECORD-1 trials. mo, months; NA, not available; PFS, progression-free survival; wk, weeks.

40%—less than the 59% reported in the BOLERO-2 trial using the same regimen [4, 11]. Ongoing prospective studies (NCT02376985, NCT02229136, NCT02015559, NCT02069093, and NCT02273752) will determine the value of dental/oral hygiene measures, mucoadhesive oral wound rinses, pharmacokinetic-based dose adjustments, and prophylactic steroid-based mouthwash in reducing the incidence of everolimus-induced stomatitis and improving its management [12].

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